114: Assessing a polygenic risk score for Parkinson's disease in 22q11.2 deletion syndrome

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Background: The 22q11.2 microdeletion confers an elevated risk of parkinsonism, particularly early-onset Parkinson's disease (PD). The extent to which common genetic variation associated with idiopathic PD modifies parkinsonism risk in 22q11.2 deletion syndrome (22q11.2DS) remains unclear. **Methods:** We performed an out-of-sample PD polygenic risk score (PD-PRS) analysis in 205 unrelated adults with a typical 22q11.2 microdeletion (31 parkinsonism-cases, 174 controls) with available genome sequencing and movement disorder phenotype data. Allele-weighted risk scores were calculated in PLINK using a previously validated PD-PRS (PGS000903) comprising 1,392 single nucleotide polymorphisms (SNPs). Between-group comparisons were conducted in the full sample and in an age-adjusted subsample (controls $\geq$ 30 years). Association between PD-PRS and parkinsonism status was evaluated using logistic regression models adjusting for age, ancestry, and psychotic illness. Sensitivity analyses were performed using a genome-wide significant 90-variant PD-PRS (PGS000902; 37 overlapping SNPs). **Results:** Standardized PD-PRS did not differ significantly between individuals with and without parkinsonism in the full sample ($p = 0.85$) or age-adjusted sample ($p = 0.96$). Logistic regression revealed no significant association between PD-PRS and parkinsonism (unadjusted OR 0.96, 95% CI 0.66–1.41; adjusted OR 0.90, 95% CI 0.53–1.53; p for both models >0.5). Inclusion of PD-PRS in the full model increased explained variance by <2% (ΔNagelkerke $R^2 \leq 0.002$). Findings were consistent using the 90-variant PD-PRS. **Conclusions:** Interim analyses suggest the possibility that PD-PRS derived from a large population-based GWAS does not significantly modify parkinsonism risk in adults with a typical 22q11.2 microdeletion. These preliminary findings may indicate that PD-associated common genetic variation contribute minimally to motor expression in the presence of a high-impact variant such as 22q11.2 microdeletion. The genetic architecture of 22q11.2DS-associated (early-onset) parkinsonism may differ from that of idiopathic (late-onset) PD. Our findings support investigation of alternative genetic risk modifiers, including additional rare variants.